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FOOD AND DRUG ADMINISTRATION

CENTER FOR VETERINARY MEDICINE

GENERAL PUBLIC MEETING

Welcome and Introduction

by Dr. Stephen Sundlof,

Director, Center for Veterinary Medicine

(1:15 p.m.)

DR. SUNDLOF: I think we're all hooked up here and ready to go. Good afternoon, everybody. I want to welcome everybody to this community that for us is very important. We're really glad to see that there is a lot of interest out there, because we're talking about the future today and we need all the best input that we can get. If we can get the slides going --.

Before I get started, let me introduce you to some of the people that were responsible for making this happen today. I am Steve Sundlof. I am the Center Director of CVM. We have Dr. Sharon Thompson who has taken on the responsibility for coordinating our activities in the area of antimicrobial resistance. To her left is Jim Heslin. Jim is going to serve as our facilitator to make sure that we have a productive discussion this afternoon, because we have a lot of information that we need to get out and on the table within a very short period of time. Also Jon Scheid who has been responsible for putting together some of the slide presentations. We will be working to try and capture some of the thoughts that surface here this afternoon. Also assisting him is Joann Kla, and finally, Aleta Sindelar who has been one of the people that's been instrumental in making

sure this whole thing would come off. We want to thank them, and again, welcome to everybody.

I understand that there are some people who were intending to be at this meeting and didn't make it because of weather. So what we intend to do is provide as much of the information here today that we discuss to anybody who is interested and allow them to comment to the docket.

(Slide)

DR. SUNDLOF: Okay. The objectives of this meeting then are to gather comments about the next meetings. There's two meetings that we are going to have in the future, the risk assessment and thresholds. Well, risk assessment and threshold will be covered in the meeting on December 9th and 10th, and we want to make sure that we surface what are the appropriate issues to discuss at this meeting, who the experts are that will need to be included in the meeting so that we get the best possible advice.

The agenda. We would like your advice in helping us set the agenda for this meeting, and all of the comments from this meeting will be included in the docket, which is that docket number there (indicating) if you would like to write that down. Any comments that you think of after this meeting can be submitted to the docket.

There is another meeting that will be held in February, February 22nd and 23rd. That will be looking at the issue of pre-approval studies. So there's actually two meetings. The most immediate one is going to be the one on thresholds, and in

there will be a risk assessment.

Let me just say that the bottom bullet there says we are not trying to -- the purpose of this meeting is not to reach consensus; the purpose of the meeting is to get people's comments. This is a nondecisional meeting. This meeting is for information gathering. So please keep that in mind. Legally we cannot have a meeting at this time that would try and develop consensus. So this is under the Federal Advisory Committee Act. This is how we have to be structured.

(Slide)

DR. SUNDLOF: Regulatory course. A little background in history on this. The issue of antimicrobial resistance has not been a subject that lends itself easily to regulation and the regulatory process. It is a very complicated subject. It is virtually impossible to predict ahead of time. FDA in the past, although we have struggled with this issue quite a bit, have not really proposed a regulatory scheme for dealing with the issue of antimicrobial resistance for the reasons I have just mentioned, scientific complexity, the fact that there is a lot of information that we just don't have that would be extremely useful in developing a regulatory approach to this, but we decided that now is the time to move forward on this despite all of the obstacles. We think this is important, because as I indicated, there has been lack of information. We are starting to see more information now, some good scientific studies out there that definitely point to an association between the use of antimicrobials in animals and certain foodborne infections in

people. So based on the mounting evidence, we think it is time to try and move forward. We also recognize that there certainly is a need for antimicrobial drugs in animals, and we somehow have to strike the appropriate balance between our responsibilities to public health while making sure that there is a rational avenue that will allow these drugs to be used under whatever conditions are appropriate in food animals.

(Slide)

DR. SUNDLOF: We declared publicly last November that we believe the time has come for the FDA to take a different approach to really start concentrating on the issue of antimicrobial resistance in the regulation of animal drugs. That appeared in *The Federal Register* last November, and it is also on our web page. So anybody who wants to find that particular document --. Basically, it said that for all uses of all antimicrobials, not just subtherapeutic use, but therapeutic uses as well, but we needed some additional information. We needed information on resistance and also increased pathogen load that sometimes occurs following the administration of antibiotic.

(Slide)

DR. SUNDLOF: In December of last year, we subsequently issued a Framework Document. Now the Framework Document, it's got a big long name and I can't even recall it, so we just call it the Framework Document. It basically lays out the Center's thinking about -- not only Center but the Agency. We did discuss this within the FDA and other Centers within the FDA, and it basically said look, when we got all of our best people together

that had knowledge on this issue, this is the kind of regulatory approach we thought made the most sense, and we would like to let the rest of the world now look at that and comment on it and tell us where we got it right, where we got it wrong, things that we need to change. It was a document that was meant to just give the public our best opinion at the time as to what we thought was a rational regulatory approach.

Subsequent to that announcement, we had a Veterinarian Medicine Advisory Committee that met in January of last year who further discussed this. We got a lot more discussion going at that point, but it was truly meant to be a discussion piece. We indicated that we wanted a lot of comments on that and that we would revise our approach based on the comments. I can tell you that we will have before the December meeting, we should have those comments available and published. Some of them are up on the home page right now.

(Slide)

DR. SUNDLOF: But the Framework concepts basically looked at what is the public health risk. It is a risk-based approach to dealing with the regulation of antimicrobials in food animals. We introduced a concept of resistance and monitoring thresholds that I'll talk about in a few seconds, and we introduced the concept of having some pre-approval studies that would give us some predictive value about what might happen once the antimicrobial is actually out there and in use, what is the likelihood that resistance will develop, how fast, and in which particular organism.

(Slide)

DR. SUNDLOF: We indicated that we were trying to use a risk-based approach in dealing with this subject. If you use risk analysis terminology, one of the things you have to do is you have to characterize the risk. The risk characterization is the product of the hazard times the exposure, and so you have to define both hazard and exposure.

Hazard in this case would be the impact on public health should that drug no longer be useful because of the development of resistance. That is the harm part. That is the hazard part. So it is based on the importance of the antimicrobial in human medicine. Not all antimicrobials are equally important, and we want to identify those that are most critical need. Then we wanted to look at the human exposure that might be, that we would expect to occur from the use of these drugs in animals and what -- how likely would humans be exposed to pathogenic microorganisms that were resistant to these drugs as a result of the use in animals, what exposure would be expect.

Then we said that based on these concepts, we would set some pre-approval and post-approval requirements based on how these fell out. So if you had a large hazard with a high exposure, obviously the regulatory requirements would be greater than for those drugs for which there is low exposure, low potential exposure that may not be as important in human medicine.

(Slide)

DR. SUNDLOF: Then we talked a little bit in the

Framework about risk management. This is really what we are going to be talking about for the December 9th and 10th meeting, setting resistance and monitoring thresholds. These are risk management in that they lay out ahead of the approval process at what point we would consider the drug to no longer be safe. So the resistance threshold is that point at which it would trigger some regulatory action.

The monitoring threshold is some earlier warning along the line before you get to resistance, to the development of resistance. It would mark those places where we would want to take additional actions, but not necessarily withdrawing the product, for instance. Those would be where we would intervene, such things as further studies to determine what particular practices might be driving the development of resistance, may require some changes in the --- another thing.

(Slide)

DR. SUNDLOF: In addition, depending upon the drug's category, where it falls out on this matrix, we may require pre-approval studies. That will the subject of the meeting in February. We may require some additional post-approval monitoring, other than the NARMS monitoring. That, again, needs to be worked out.

(Slide)

DR. SUNDLOF: So, in comments so far we have heard very loudly that there needs to be a lot of stakeholder involvement on this issue. I think everybody --- has said that they want to be involved in it. The decisions are risk-based, based clearly in

science, that there is definitely a need to clarify the categorization of drugs. Everybody I think has been very supportive of the National Antimicrobial Resistance Monitoring System, and that that program in particular should be supported to give us the greatest surveillance tool that we can put together. As I indicated, we will be publishing these comments before the December 9th and 10th meeting, so everybody should have a chance to read through the comments.

(Slide)

DR. SUNDLOF: Again, I want to thank you all for attending. I am going to ask Dr. Thompson now to come up now and present some comments, and then we will go into an open session where we will beseech your input. Then I will try to make some feeble attempt at summarizing the comments at the end of the day, and then we and adjourn by 5:00 o'clock. So again, thank you for coming.

Overview of Plans for the Workshops on Risk Assessment/Thresholds and Pre-approval Studies

Presentation by Dr. Sharon Thompson

DR. THOMPSON: Good afternoon. I am going to try to give you a little bit of an overview of our plans for both of the upcoming scientific meetings with the hope that this will really allow you to give us your feedback, give more targeted feedback to us. Certainly, as Dr. Sundlof indicated, I understood some people were delayed or would not be able to come today, so I will try to make copies of my slides available on our home page so people can see those, and they may be able to send us comments

afterwards to the docket targeted to some of the points we have highlighted here.

(Slide)

DR. THOMPSON: So as Dr. Sundlof mentioned, we basically are planning two meetings. The first meeting will be held the 9th and 10th of December and will focus on risk assessment and the establishment of thresholds. The second meeting will be held on February 22nd and 23rd of next year and will look at pre-approval studies.

(Slide)

DR. THOMPSON: In general, just to make some comments about our plans for the meetings, both of the meetings are scheduled to be held here in the DoubleTree. They are scheduled to go for the full day from 9:00 to 5:00. We are currently planning to structure the meeting with both plenary and breakout sessions, where we would have a plenary with everyone in attendance and then divide into as much as three groups, three breakout sessions to look at specific scientific issues. Certainly I would like to invite you all to consider this, whether this is an appropriate way to address these meeting topics or whether it would be better to hold these meetings in one continuous plenary session, but this at least is what we have planned to this point in time.

The purpose of the meetings is to seek input from experts on the approaches that CVM will outline at the meeting, and then also to ask for suggestions on alternative approaches, maybe things that we haven't thought of to this point in time.

As we get closer to the meeting dates, we do plan to make more information, meeting agendas, potential discussion documents, the risk assessment which I will discuss in a minute, will all be made available through our home page. So I suggest that you do consult that regularly.

(Slide)

DR. THOMPSON: As Dr. Sundlof mentioned today, the purpose of the meeting is to seek input specifically on the issues that we will be outlining, what are the appropriate issues to be considered underneath both of the scientific workshops, suggestions on experts that CVM should invite. We have provided for a certain amount of experts. We do have funds available, if we do have nominations for experts, to pay for those people's expenses to attend the meeting.

Suggestion on agenda items. Are there specific topics you would like to see discussed? Then the format as I mentioned, in terms of the plenary and the breakout sessions, whether you think that is appropriate.

If you have additional comments following today, as Dr. Sundlof mentioned, we do have a docket that is being created and you can submit comments directly to that. Especially with respect to the December meeting since it is coming up so quickly, the sooner you can get us your comments, that would be appreciated, because that will really enable us to move forward on planning that meeting.

(Slide)

DR. THOMPSON: Okay. So let me talk first about the

Risk Assessment and the Establishment of Thresholds Meeting. The purpose of this meeting is to discuss CVM's risk assessment model, specifically to evaluate the risk to human health from resistant foodborne pathogens associated with the use of antimicrobials in food animals, and also to discuss our current thinking as to how we would use this model to help us establish resistance and monitoring thresholds in food animals.

(Slide)

DR. THOMPSON: I want to make a few comments about the risk assessment. I think this will be helpful to people who are not familiar with what is being discussed here so that you can more appropriately give us our feedback. The risk assessment is basically modeling the risk of increased duration of illness due to resistant *Campylobacter* infections associated with the use of fluoroquinolones in chicken. The model will allow us to relate the prevalence of resistance *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of resistance *Campylobacter* in chickens. I will come back to this, because this is really key when we talk about the establishment of thresholds, the ability to make this connection.

(Slide)

DR. THOMPSON: I have had many people ask me why did we pick this specific example, why are we looking at fluoroquinolone resistance in *Campylobacter* in chickens. Basically, to model something you do have to pick a specific case; you can't just model in general what is the impact of resistant foodborne disease.

(End Tape 1, Begin Tape 2)

DR. THOMPSON: -- specific example, and we picked *Campylobacter* specifically because one -- it's not listed on the slide, it is because we felt that there would be data available to analyze this situation, and since there were a number of ongoing studies, case control studies looking into this issue, it really would provide the data to help us to model this that we felt would be successfully.

In addition, we felt that *Campylobacter* is a very large foodborne illness problem, and so it was an appropriate thing to start with. In chicken, if you look at *Campylobacter* in terms of the source of *Campylobacter*, chicken in the largest source, and then certainly, fluoroquinolone is a -- fluoroquinolones are an important drug in human medicine. It is a sensitive issue, so we also felt that this was a good reason to start with this particular example.

Then in terms of the direct versus indirect transfer of resistance, a direct transfer of resistance is certainly easier to attack, and we felt that that was more appropriate to model first, although we are, and I will mention later, looking at the indirect transfer issues as well.

(Slide)

DR. THOMPSON: So the problem that we are facing or we are examining in this risk assessment is that basically poultry -- we see that poultry get a disease, they get colibacillosis, and then we are looking at treating most of those sick animals with a fluoroquinolone, and as a result, there is a

potential for a fluoroquinolone resistance *Campylobacter* to proliferate in the poultry gut. Humans can then be infected by fluoroquinolone resistance pathogen by consumption of poultry. Then in the scenario that we are examining here, infected people may not respond to a fluoroquinolone if administered when they go into the hospital or physician to be treated.

(Slide)

DR. THOMPSON: So we can estimate the current level of *Campylobacter* in broilers. We can also estimate the number of people who become ill from these pathogens. We can therefore estimate the relationship between the level of *Campylobacter* in chickens and the number of people who become ill from these pathogens.

The data for really the whole risk assessment comes from several different national surveys. I have mentioned some of the information here, NARMS, CDC case control studies, and Food Mat, although we are also looking at some published literature studies as well.

(Slide)

DR. THOMPSON: We can also relate the incidence of *Campylobacter* resistance infection in humans to the resistance pathogen prevalence in poultry. This is really key when we look at the establishment of thresholds. The risk assessment also looks at the human cases that sought care, were prescribed fluoroquinolones and were resistant to the fluoroquinolone. The risk assessment model is set up to assess the human health impact of infection being resistant versus susceptible, and that's what

we are really looking at in terms of potential harm.

(Slide)

DR. THOMPSON: So in the establishment of thresholds, CVM must really determine at what level is any identified human health impact unacceptable. We can look at this. The model is set up to look at days of illness, days of enteric illness. We can also look at it from the perspective of probability of harm, what is the probability that somebody would be affected by a resistant pathogen.

Once we determine what is acceptable in terms of human health impact, and we have to look at this really in the context of the Reasonable Certainty of No Harm Standard, once we determine that, what is the unacceptable human health impact, the model will allow us to relate that back to a resistance prevalence in chickens. So we can say, okay, above a certain level of resistance in chickens, that is an unacceptable -- we would see an unacceptable human health impact. That would allow us to determine a resistance threshold in chickens.

We can also use this to establish a monitoring threshold. That would basically be a more conservative level. It would be an early warning system to allow us to monitor that and take action, mitigation action, when that level is being approached.

(Slide)

DR. THOMPSON: Basically, I started out by saying that the model was set up to look at a specific example, the *Campylobacter* chickens and fluoroquinolones, but it is designed

to be able to be extrapolated to other antimicrobial foodborne pathogen combinations, with additional data. It is important to note, however, that there may be certain antimicrobial pathogen combinations for which data are lacking. In these cases, CVM must make certain assumptions to establish a threshold that conservatively will protect public health. So this is certainly an area where additional data would help us to be potentially less conservative in any number that we would set.

Our current plan is to release the risk assessment in advance of the December meeting. I mean it will be released. Our intention is to publish that on our web page. We may also publish it in *The Federal Register*. At least we will put a notice out in *The Federal Register* saying that it is available.

I started out by saying we picked a direct foodborne pathogen resistance issue to model because the indirect was more difficult, but we are beginning to look at that issue as well. We will be getting a risk assessment on that. That will not be discussed, though, at the December meeting.

(Slide)

DR. THOMPSON: Okay. So in terms of the December workshop, what are some issues that we are looking at? I basically tried to write down some different issues that I thought might be appropriate, specifically to be the subject of breakout sessions. I am going to run through these relatively quickly, and I would certainly welcome your comment on any of these ideas that are being proposed or certainly to give us other ideas as well.

One area would be to discuss the model itself, what are comments on the limitations of the model, identification of any significant data gaps in the model, comments on positive aspects of the model and also certainly aspects that you recommend that need to be changed, and then how can we use the model to help the industry reduce the risk, the level of risk that is identified.

Another area of interest, because this is relatively an innovative approach to modeling this issue, so a thought would be to have a session on mathematics, the mathematics of the model.

Use of the model for other antimicrobial foodborne pathogen combinations, how would we do that, what would be the assumptions we would potentially need to look at to allow us to make that extrapolation.

(Slide)

DR. THOMPSON: I highlighted the mechanisms we plan to use this to establish thresholds, how would we do this, how should this relate to the Reasonable Certainty of No Harm Standard. When we do put the model out, we will discuss this in the risk assessment, but certainly we would be looking for feedback on that; is that an appropriate standard to use, for instance, are there other appropriate standards, have we chosen the right level.

Then, how should we view the population of concern? Depending on how you define the population of concern, it will have a big impact on the level of risk that is identified. So should we look at it from the perspective of the entire U.S. population, those individuals with *Campylobacter*, or more

specifically or narrowly those seeking care and requiring treatment for resistant pathogens? So obviously that is the smallest population of all.

Then how can industry assist the Agency in obtaining data to reduce the uncertainty in the model? We will highlight that, the areas of the model where we really could use additional data, where we are most confident about the data that is there and where we are the least confident.

Then potentially another session could be on appropriate mitigation actions to be taken when monitoring thresholds are reached.

So just to go back to the start, we really are seeking input on the appropriate issues. Are some of these that I have highlighted, are these the right issues, are there others that should be included? Suggestions on experts who really can give us input, scientific input on these areas. Suggestions on additional agenda topics. The format, is breakout sessions a good approach?

(Slide)

DR. THOMPSON: I am going to move to the workshop on pre-approval studies. In this you will see there is a lot less thought at this point in time on this workshop, and that is because we have a little bit longer to plan for it. But the plan of this workshop is to discuss our thinking on the appropriate design of pre-approval studies in food animals to model the rate and extent of resistance development.

(Slide)

DR. THOMPSON: We are really looking at three basic areas of concern. We are looking at the potential transfer of resistance foodborne pathogens to humans, the transfer of resistant determinants from a foodborne bacteria to a pathogen within the human GI tract, and then also pathogen load, increase in pathogen load in the target animal as a result of treatment with a new animal drug, and basically looking at not only the increase in the total population of shed pathogens, but also looking at the fractions in terms of the population of pathogen shed.

(Slide)

DR. THOMPSON: CVM basically is approaching these concerns at this point in time with the design of pre-approval studies. The pre-approval studies would be used to predict the time it would take under actual use conditions to see changes in susceptibility to the drug, and the studies would also look at the magnitude of the changes in susceptibility to the drug. The final area is looking at pathogen load, determining the potential of the drug to increase pathogen load in the target animal.

(Slide)

DR. THOMPSON: In addition to the general questions on issues, format, agenda and experts, with respect to the Pre-Approval Studies Workshop, we would really like to ask for comment on whether or not we should plan to hold two separate workshops, one to look at resistance and one to look at pathogen load, or whether both of these topics should be dealt with in the February meeting.

The pros of looking at both topics is obviously we would open the discussion on both early. So that is a definite advantage. There is some thought that that may also facilitate the design of study protocols to address both of these topics in one study rather than two separate studies. So we feel that that is an advantage.

Our concern, however, is that trying to deal with both of these topics in only two days we may end up giving short shrift to the topics, that we really wouldn't come up with any recommendations at the end of the meeting. Also, as a result of that, we may actually delay our overall guidance with respect to these areas because we have not dealt with either of the topics adequately in this one meeting. So I would certainly like to hear some feedback on this, whether people think we should deal with this in one meeting or two meetings, and that will help us make a decision as to how we move forward.

So I am going to stop there, and I apologize for taking a little bit longer than I had initially planned on the agenda, but I did feel it would be helpful to go over the risk assessment and give you some sense of what that is going to do and how we would use that to establish thresholds. So I am going to finish my remarks and we are going to go ahead and open up -- I am going to turn it over to Jim Heslin to help us manage the public commentary. Thank you.

Public Comments on Risk Assessment and the Establishment of Resistance Thresholds and Pre-Approval Studies Workshops

Moderated by Mr. Jim Heslin

MR. HESLIN: Good afternoon. In just a minute I will invite you forward to make your comments, but there are a couple things I wanted to go over first. Just to restate that the purpose here is to get comments and input on these two, on the design and development of two scientific workshops. To that end, we are looking for the scope, the format of the workshop, comments on the issues, the possibility of experts that could be involved in this process. So there is really a broad area here that is open for you to comment on, and this is an opportunity for you to let the Center for Veterinary Medicine hear your thoughts on how these workshops should be designed. Dr. Sundlof and Dr. Thompson may ask questions for clarity, but primarily their role is to listen to your comments and suggestions.

There are three microphones across the front of the room. You can use whatever one you choose. Be careful. I think the cords are pretty well taped down, but just watch yourself as you go to the microphone.

If you have additional comments to submit, for those of you who have picked up the handout "CVM Update," listed in there is the docket number and the address to send any written comments to.

In order to get a better sense of how much time we can allot both for the first part of the discussion which has to do with the risk assessment and establishment of resistance threshold workshop, that is one piece. Then we are going to take a break and then come back to pre-approval studies in

antimicrobial resistance. So try to limit your comments to the appropriate workshop in each phase here. Regarding the first workshop, how many individuals or organizations intend to make comments?

(Show of hands)

MR. HESLIN: Okay. All right. Well, I think we were going to try to limit this to five minutes for your comments. I will give you a heads-up when you have about a minute left so you can close that out. I would ask that when you come forward you identify yourself and your organization. Okay. Any questions about the process?

(No audible response)

MR. HESLIN: Okay. Who is first? I did see some hands raised. Yes.

DR. CARNEVALE: Thank you. I am Dr. Richard Carnevale. I am Vice President for Scientific, Regulatory and International Affairs for the Animal Health Institute. AHI represents manufacturers of pharmaceuticals, feed additives and biological products for use by the animal community.

On behalf of the Institute and its member companies, we appreciate the opportunity to appear before you today to provide our views on CVM's upcoming workshops on risk assessment and the establishment of resistant thresholds and pre-approval studies for antimicrobial resistance.

In addition to our comments today, I also have prepared remarks which I would like to submit for the record.

(Document Submitted, See Appendix)

DR. CARNEVALE: We will also provide comments later as to our recommendations for experts that might be applicable to each of the various components of the planned workshop.

AHI recommends a workshop format that provides participants with a briefing on the critical issues impacting and influencing the topics under discussion followed by breakout sessions to examine simultaneously multiple topics by appropriate experts, and a closing session for bringing together the various elements.

Additionally, we would encourage CVM to begin each workshop with a clear statement of the purpose of the workshop, what they envision as the end product of the workshop, and what next steps will be after the conclusion of the program.

AHI believes a general discussion of the application of and differences between risk assessment and risk management would be an important introductory session to be addressed in the plenary. Another key topic for the plenary is the area of microbiological breakpoints and how they are usually determined and used by the medical community.

AHI recommends, further, the following topics for discussion by experts and workshop participants during the breakouts, and I might add that a number of these recommendations tie very closely with ones Dr. Thompson has already recommended: first, an analysis of the components of the CVM Risk Assessment Model and how probability estimates have been applied to the populations at risk; a discussion of the use of in vitro sensitivity data, susceptibility data, and breakpoints as

reliable indicators for predicting human health impact; an examination of how to define both a monitoring and a resistance threshold and how they would be evaluated and enforced; a discussion of the possible mitigation steps if a threshold is reached; since a risk assessment is a dynamic process, a discussion of how ongoing changes could be evaluated and incorporated into the risk assessment model, including how the model might be applied to existing products; and finally, a review including both policy and legal issues of the application of the standard "Reasonable Certainty of No Harm." We believe this is a critical discussion, since this standard is the foundation for setting thresholds. We believe there are valid questions as to whether the standard, as applied to the approval process, is properly applicable to actions the FDA may take in attempting to control antimicrobial resistance.

As I said, we will submit formal comments for the record, and we will follow it up later this week with recommendation on experts. Thank you for your time.

MR. HESLIN: Thank you. Any questions of clarity?

(No audible response)

MR. HESLIN: Okay. Yes.

MR. WOOD: I am Richard Wood, Director of Food Animal Concerns Trust. We do not have formal comments to present today, but I have some informal comments that I would like to make in reference to what has just been presented here and to the materials and perspectives that were offered in *The Federal Register*.

We have been very concerned, as others have been I am sure, about what the status is on the implementation of this Framework Document. I remember when it was first presented and then at the first public meeting on this last January, it was our impression that implementation of this document would happen in a very timely fashion, and even April was talked about as a target date for a following guidance document on this question. We support that continued sense of urgency. We are dealing with situations that do threaten public health, and any further delay really puts that public health at risk. So we would hope that, and I came to this meeting with a deep concern that the steps would be steps that were scientific steps, yes, but also perhaps steps that would further express the science of delay, and that really cannot happen. What Dr. Thompson laid out here I think was a procedure that might move us forward and might hasten the time when we actually do see a Framework implemented, and I appreciate that description that you provided us, and that would lead the comments particularly dealing with pathogen loads --- given the next section.

But also because of the delay and our concern as a consumer organization and a group also that focuses on on-farm management strategies, we are deeply concerned that any next steps be laid out have a high degree of public accountability laid into -- built into them, so that questions be addressed as to who's in charge of this process, who are the key actors that we can turn to who are making the decisions, what are the deadlines that we can expect that will be met, when will we see

the questions that we identify at these ensuing workshops answered, and when will we have a report back in terms of the results of these studies.

I really appreciated hearing that we are going to finally see the comments that many of this in this room submitted months ago, and we have been wondering when we were going to see those comments so that we could view how others were responding to this issue. So that becomes a very important part of the whole public accountability. I am concerned --

MR. HESLIN: ---

MR. WOOD: I see --- giving me a minute.

MR. HESLIN: The accountability piece, is that part of the workshop? Are you proposing that as part of the workshop?

MR. WOOD: I think, yes. I think at the workshop, I think that items -- a part of the workshop ought to identify what kind of accountability we would like to see from CVM in terms of what we expect to be fulfilled and what should be publicly out there in front of us in terms of shared deadlines. I mean, we shouldn't be setting the deadlines, but I want to know what the framework is for the deadlines. I want to know, I think we ought to know, you know, when are we going to know who is making those decisions and when those decisions will be published and a part of the public record.

I am concerned, and this is -- I am not a scientist, as I am sure you recognize, but I am concerned about the risk assessment. On one hand, I am heartened by the risk assessment focusing on fluoroquinolones in relationship to *Campylobacter*

resistant bacteria because studies are showing that this is a high risk area, but we're looking at here a Category I drug, if we were to impose the Framework Document. For a group such as ours, Category I drugs, we're really even questioning whether there should be a Category I in the Framework Document. By using fluoroquinolones as the example par excellence, is there some implicit approval of its use and providing mechanisms to see how it might be used in an efficacious way, when in fact some basic questions as to whether or not that question should be on the table in and of itself should be addressed? So a part of the workshop might be to look at the very nature and substance of the risk assessment model itself in terms of the drug choice and its focus for our own debate.

We have participated in -- finally, in terms of the risk assessment, we would hope that the question of what data is needed would be clearly discussed. We agreed with the parts of the Framework Document that said that we do need to have drug sale and use data, and we would hope that in this risk assessment that is being completed that drug use and sale data would be a part of that fluoroquinolone study as well.

MR. HESLIN: You have about a minute left.

MR. WOOD: Okay. Thank you. In terms of thresholds, again, there would be questions of public accountability clearly identifying who is going to be at the table when those thresholds -- or what types of people, what categories, what groups of people would be at the table when those threshold decisions are actually made in this risk management model. We

would be concerned that consumer representatives are a part of that and also which experts would be there. We would like to be a part of the discussion of developing that list and appreciate the opportunity to develop that list as others have been offered that as well.

Regarding the format, we have been through several now workshops where the FDA has been one of the leaders where we have had breakout groups and round tables. We have also in the past, all of us in the room I am sure have, been a part of meetings where we have all sat around one big table. Certainly the small breakout rooms and tables are more inclusive in terms of sharing information, but at some point in these workshops, I would hope that we would come to one big table where comments and debate and discussion would be a part of the public record and where together we could come to consensus, as opposed to having eight different consensuses (sic) around eight different tables. That kind of discussion is very important I think to any kind of work that we come to from all of our various vantage points. Thank you.

MR. HESLIN: Thank you. Anyone else with comments on this particular workshop that is being proposed? Yes.

MR. DODEMAIDE: Good afternoon. My name is Robert Dodemaide. I work for Hoechst Roussel VET in Clinton, New Jersey, but I am speaking personally. At this forthcoming workshop in December, I would dearly like to have included amongst the invited experts people such as the bovine practitioners, the swine practitioners, the poultry pathologists,

those specialist groups, because I feel that each of those groups has issued its own steps in order to lessen the risk of the transference of resistance factors from animals to either zoonotic pathogens or to other organisms which might infect the human gut. So I urge CVM to consider those specialist groups who I think can have -- can give us a lot of input on steps that are required to help assess the risk and to manage the risk. I think with those groups at the table we will have a far better idea about what's required. If those groups are absent, I think a lot will be missing and we could well come to the wrong conclusions. Thank you.

MR. HESLIN: Thank you. Yes.

MR. SCHILARK: I am Tom Schilark. I with the Lanco Animal Health. The comments that I wish to contribute would be made from the standpoint of the National Committee on Clinical Laboratory Standards. This is a group of which I chair the Veterinary Antimicrobial Susceptibility Testing Subcommittee. This particular organization is involved with setting breakpoints as well as setting the methodology and quality control for conducting in vitro susceptibility testing. The organization is national in scope. It has international outreach as well.

In addition to the veterinary side which is just beginning, there is also a very long history of this sort of thing with the human antibiotics. I think as we move forward it would be incumbent upon the workshop to have a presentation from members of the NCCLS, perhaps both from the human as well as the veterinary sides of things, to lay out what is available as far

as methodology for laboratories, as far as breakpoints are determined and how these may be used in actual clinical medicine practice. There is a lot of information that is generated and a lot of decisions which will be made based upon these MICs, so I think as a way to start a foundation for discussion, some of those sorts of things should be brought forward. Thank you.

MR. HESLIN: Thank you. Yes.

DR. LEIBERMAN: Hi. My name is Patti Leiberman from the Center for Science and Public Interest, and I want to also speak sort of casually today. I want to first of all reiterate some of the comments that Rich Wood made from FACT that CSPI is concerned about, the fact that this is a very painfully slow process. We are concerned that CVM doesn't feel the same urgency that is felt in the consumer groups, that it's been 10 months since putting out the Framework, and this schedule calls for only meetings and discussions through February. In the meantime, we have the CVM approving new combination drugs that include antibiotics such as virginiamycin while we have a petition pending that's been submitted by CSPI and 40 other consumer and health groups, and new CDC data on resistance is relevant to that.

Now, we have some general concerns about the Framework that we have made in our comments before. One has to do with the categorization of the kinds of drugs. It seems difficult for us to talk about how we would set thresholds for these things if we don't have the categorization done ahead of time, before we discuss it, because as Rich said, some of these Category I drugs

we feel really shouldn't even be -- I mean, there might be no threshold of resistance that would be acceptable to us.

We have concerns about waiting for a risk assessment and waiting for data when we know that the drug companies have not been forthcoming in giving drug use information. Perhaps they will change their tradition of not giving that information.

We wanted to make sure that the upcoming scientific meetings really were mostly composed with people who are experts in public health, microbiologists, also with some input from consumer groups, but for the thresholds, that the focus needs to -- especially for the meeting with thresholds, the focus of the expertise should be on people who are thinking of human health, with animal health obviously being a factor. We suggest considering some of the experts, the scientific expertise from the European community where they have made policy decisions with the data that they have to try to move forward on this issue. Thanks very much.

MR. HESLIN: Thank you. Anyone else with comments on this particular workshop? Yes.

DR. SHELDON: How do you do. My name is Al Sheldon. I am a team leader in the Division of Antiinfective Drug Products. We are responsible for the review of antibiotic new drug applications with -- that are used in humans. I would like to reiterate the last point that was made about using experts from the scientific community in Europe who have done a lot of work to try to identify some of the risk factors associated with use of antibiotics, not only in animals but also in human medicine, and

to invite individuals from the human community to try to understand the risk factors that have been defined there also, because we are in fact not independent of each other but actually occupy the same ecological niches, and we need to have an understanding of how the use of antibiotics and the ecology niche which we all occupy is playing a part in antibiotic resistance.

Secondly, I would like to note that the FDA, the microbiologists in the Division where I work, are responsible for the setting of interpretive criteria, that is breakpoints, that are used in package inserts. I am a member of the NCCLS, and I am a voting member of the AST, which is the Antibiotic Susceptibility Testing group, and I would like you to invite the FDA microbiologists to make a presentation on the establishment of interpretive criteria from the regulatory perspective within the Agency.

MR. HESLIN: Thank you. Anyone else for this round of comments? Yes.

DR. ANGULO: I am Fred Angulo from the Centers for Disease Control. I also would like to join those who have voiced support for the Framework Document and the momentum that is occurring here with the establishment of these public meetings, and I think this input is critical and essential and applaudable, although I also join with others saying that I think it would be very useful to have a vision on the implementation dates so that people could understand, at least in broad terms, when final regulations -- final implementation might be in place. I know that dates tend to change over time, but just a regular --

general thoughts on implementation would be very useful.

The specific comment is that I think much of the discussion on the Framework Document, the extremes of the discussion, could be moderated if it was clear what the categorization of the drugs were. So I think that some of the concerns that on one extreme people are concerned that all drugs used in food animals would be categorized in a high value or a low value, that once it's clear which drugs are Category I, then perhaps that the movement towards implementing the Framework might proceed anew. So I would encourage holding the necessary meeting to categorize the drugs in the near term, and perhaps even before the December meeting have a straw man categorization of the drugs which would help some of the discussion at the December meeting.

MR. HESLIN: Thank you. Yes.

MR. UNOWSKI: Joe Unowski. I am a reviewer in the Department of Antiinfective Drugs Products working with Dr. Sheldon. It's concerning the categorization of drugs. Genetic resistance is most often linked genetically, and I think we should have some genetic experts to discuss the problem of carrying along other drug resistances besides the ones we are majorly concerned with, because resistance to fluoroquinolones can prolong resistance to other drugs, for example. So I would like to see some genetic experts to discuss this.

MR. HESLIN: Thank you. Any other comments at this point?

(No audible response)

MR. HESLIN: Okay. If I could get a show of hands as to the number of people who want to make comments for the Pre-Approval Studies Workshop.

(Show of hands)

MR. HESLIN: It looks like just one.

(Show of hands)

MR. HESLIN: Just a couple folks. Should we take a break and come back to that, or just continue on?

(Brief recess)

MR. HESLIN: Yes. I think there were two that raised their hand. Okay. I think after the comments Dr. Sundlof and Dr. Thompson will need a few minutes to get their thoughts together on the summary of the discussion and the next steps, so at that point we can take a quick break.

Okay. Shifting gears to the Pre-Approval Studies in Antimicrobial Resistance Workshop. Did someone here raise their hand? Yes. If you could reintroduce yourself.

DR. CARNEVALE: Yes. I am Dr. Rich Carnevale again with the AHI. Our comments on pre-approval will be very brief because we haven't really had a chance to think about that as much as we have had the threshold workshop. On the question with regard to whether there needs to be a separate workshop on pathogen load, I don't have a formal opinion on that at the moment. It may have some merit to have a separate workshop. We will have to go back and think about that, to that specific question that Dr. Thompson posed.

A couple of thoughts, though. We do think that a

workshop on pre-approval needs to right at the beginning state the real purpose for the pre-approval studies and exactly what value the pre-approval studies have and how they will be used in the evaluation process. We think that is very important, because I know AHI in looking at this Framework Document has been a bit confused at times of how all the pieces fit together and what value all the pieces have in the process of evaluating antimicrobial resistance.

A couple of specific points we would make that needs to be included in the workshop, we believe, is there have been over the years a requirement for microbiological studies under 21CFR55815 for the continuous feed additive products, as they say, continuous feed additive products, longer than 14 days I believe in duration. There is a lot of experience with those studies, both the industry and the people that conduct those for the industry, and we think a presentation by people that have conducted those studies as to the value of those studies or the lack of value of those studies as the case may be, and what they have shown from conducting them over the last 10 to 15 years. So that is a key part of I think this workshop, is to have that right at the beginning.

Also, we think that there is a lot of data that is currently collected by pharmaceutical companies, both the human side of the company as well as the veterinary side of the company, on microbiologic information and the microbiologic qualities of the products that are being -- the compounds that are being discovered and developed. We think it is very

important to have an expert provide an overview of how a compound may be taken from discovery to final approval on the veterinary side to really give the audience a comprehensive picture of what really goes into a new animal drug application. We are concerned at times that there may be a lot of misinformation as to exactly what kind of data is collected and generated for antimicrobial products that go into veterinary use.

We have submitted formal comments as well, back when the Framework Document was first issued. There was a request for formal comments, and we did provide some 60, 70 pages of comments on all phases of that document. We resubmit that for your convenience. In that is a section specifically aimed at pre-approval studies with some suggestions for how pre-approval studies, if they are going to be required, might be conducted. So I submit that for your information as well, and as we get closer to that workshop, I am sure we will have further and more detailed comments to make as further information comes out. Thanks.

(Documents Submitted, See Appendix)

MR. HESLIN: Thank you. Yes.

MR. WOOD: I am Richard Wood with Food Animal Concerns Trust. My comments as well are very brief. We of course are not the experts in the new animal drug approval process, which leads to one of our first concerns, and that is that who are the experts that we put together for this and what kind of review or discussion might there be around that panel. We would be identifying some people that has come from our reading of the

scientific literature, but I think that is, for us anyway, a very critical question.

I came to this meeting not knowing what you were going to be presenting, Dr. Thompson, but one of the things on my list was a concern that the pathogen load was not being addressed. It was good to see that that side of the equation and what happens to the intestinal fluor was being put on the table. I can't answer it from our perspective whether that needs to be a part of one meeting or a second meeting. Again, I bring you our primary concern, is that we move forward, so, whatever facilitates that and causes that to happen.

Finally, more of a question than a comment on another part of this whole Framework package that may or may not be a part of either of these workshops but I think is important and does need to be addressed, is the post-approval monitoring process. It may be a part of this second workshop, if in fact post-approval monitoring is built into the drug approval process, where there are agreements made at that point, but I know there has been some discussion as to where that post-approval monitoring would take place. I think that discussion needs to be continued. I believe the Framework Document lays out that the post-approval monitoring take place perhaps on-farm. We would support that, but there are a number of issues involved in doing that would -- that deserve some discussion and consideration by all of us in this room. Thank you.

MR. HESLIN: Thank you. I think there is a gentleman who walked in just a couple of minutes ago. Here is your

opportunity to comment if you want to do so.

(No audible response)

MR. HESLIN: Okay. I think that concludes the public comment piece. Let's go ahead and take a break. Twenty minutes sound about right? Will that give you enough time?

DR. THOMPSON: Yes.

MR. HESLIN: Okay. If you want to, reconvene in 20 minutes. I believe there is coffee outside.

(Brief recess)

MR. HESLIN: Okay. If you will take your seats, we will get started again. For the remainder of the time we have here this afternoon, Dr. Sundlof and Dr. Thompson will be feeding back to you what they heard in terms of comments and suggestions on these two workshops. It is an effort to ensure clarity and understanding. If there is something you want to add to supplement, fine, but this is not a new discussion point. It is confirming what was heard earlier.

Before we do that there are two things. A question came up about the docket number and which docket number to submit the comments on each of the workshops to. Either workshop goes to the same docket number. I think there was some feeling that maybe it was just for one, and they were looking for -- somebody was looking for a docket number for the other one, but both workshops, same docket number.

Also, there were some additional comments, and I want to just open this up for a new minutes, that were sent in for Mr. Wages to make, and so we will go ahead and do that now. Just

identify yourself and your organization.

DR. WAGES: I am Dennis Wages, and I am representing the American Veterinary Medical Association. The AVMA were going to withhold their comments and basically not have any public comments that were going to be written. Certain aspects from the bovine practitioner and avian pathologists have written some, and I am just going to read them. I don't know their background, but I will read them as they have been presented to me.

The first was, "The American Association of Bovine Practitioners Committee on Pharmaceutical and Biological Issues look forward to participating in the December and February meetings related to antimicrobial resistance in food-producing animals.

"We strongly feel that the existing degree of risk of antimicrobial resistance in humans due to antimicrobial use in animals should be determined. Without an assessment of the overall risk to people of antimicrobial use in animals, monitoring of effects of policies to reduce resistance in people with changes in antimicrobial use or availability for animals would be meaningless. A reduction in risk implies that there is a value for risk.

"Likewise, a value for risk is necessary to determine the cost of interventions intended to reduce the risk. For example, if an intervention costs $10,000 and it reduced the risk from an estimated 5 work days lost per case of sickness due to antimicrobial resistance caused by antimicrobial use in food animals to 4.75 work days per case, policy makers would have to

decide if the $40,000 per week (sic) day was a good public investment." I hope you all followed that.

(Laughter)

DR. WAGES: "Similarly, thresholds should be determined based on calculations intended to show that above a certain level risk will change. If an antibiotic with an easily attainable MIC for a selected pathogen is found to have a small shift in MIC, the risk may remain constant.

"In summary, without a beginning assessment of the risk of antimicrobial resistance in humans due to the use of antimicrobials in animals, the need to establish resistance thresholds, change pre-approval studies, or the effect of any other policies to reduce risk would be difficult to measure.

"We would encourage the participation in the future meetings of Drs. Kathy Ewert and Dave Dargatz. We feel that both have demonstrated knowledge and impartial judgement important to the success of the meetings.

"The American Association of Bovine Practitioners very much looks forward to participating (sic) by member veterinarians and other experts at the December 9th and 10th and February 22nd and 23rd meetings."

Next fax. "Concerning workshops on risk assessment and establishment of resistance thresholds, this may be the place to try to get CDC and CVM to clearly articulate is there a degree of risk to human health that is or would be acceptable from the use of antimicrobials in animals. At some point such a threshold should be established.

"If we are left with the answer of 'none,' they would have full leeway to pursue any punitive programs that is politically possible. In other words, we would hope risk assessment, as it is used here, would be the assessment of overall risk. We are concerned that risk assessment by their definition what is really meant is a separate issue" -- excuse me, "is risk of reduction, which is a separate issue and changes the intention of the meeting entirely. Hopefully, Dr. Lester Crawford could speak to this from Georgetown University, or Dr. Harley Moon with his experience from the National Academy of Sciences.

"If we don't establish what is the risk, calculation of any meaningful cost benefit analysis, including environmental ramifications of poor feed conversions, increased mortality, et cetera and its effect on environment of public health, would become impossible.

"Establishment of resistance thresholds. A key issue here would be try to confine any action levels to resistance development within the veterinary community rather than the human community. Given the potential for resistance development within the human community due to the antibiotic use there, it may be inappropriate to try restriction of use of drugs in the veterinary community to try to sway the resistance development in the human community. Dr. Clyde Thornsbury may be a good reference in this area.

"Pre-approval studies in antimicrobial resistance. Information collected in these studies should focus bacteria

collected in the ready-to-eat cooked product. Collecting bacteria from the farm for this purpose is not generally germane to foodborne disease and tends to denigrate efforts within the food processing industry to control the transmission of such agents."

MR. HESLIN: You have about a minute left.

DR. WAGES: Yes, I think that's about all I got left. "CVM's position might be, if they are interested in overall environmental load of resistant organisms, to which the reply should be, trying to prove a link between veterinarian and human resistance through food supply mechanisms has been very difficult in a quantitative way and that efforts to make such a quantitation, they would be based on total environmental load" -- "being based on total environmental load, are at least premature and may be in fact irrelevant." Thank you.

MR. HESLIN: Thank you. And with that, we will transition to Dr. Sundlof who will -- I am sorry.

MR. : We have a clarifying --

MR. HESLIN: Yes. I am sorry. A question for clarity.

MS. : Yes. Was that a second set of comments? Who was that from?

DR. WAGES: That was from Dr. Larry Geinder Govermilling. He is a veterinarian in charge of -- I am sorry I didn't say that, both poultry and swine.

DR. SUNDLOF: Okay. I am going to attempt to summarize. In fact, I put down -- we had three different people taking notes, and when we compared them we all three said

different things. So I strongly encourage everybody to submit their comments in writing. I am going to try and summarize. The only way I can see to do this is just go down through the list of speakers and try and summarize what they said, and then I am going to have -- and then Dr. Thompson is going to go back and fill in some blanks where I missed issues. Then if the speaker feels that I did not accurately capture the comments, please feel free to step forward and correct the record.

The first presentation was by Dr. Richard Carnevale from the Animal Health Institute. He talked about first of all the format of the meeting and that the format should really be three different parts. First of all, there should be a briefing on the critical issues in plenary, including a discussion of risk assessment and risk management, breakpoints and their use in setting thresholds, such things as how -- well, let me go back. Then have breakout sessions, and in those breakout sessions such things as evaluating thresholds and how they would be enforced, resistance versus loss of susceptibility, how the Reasonable Certainty of No Harm Standard would be applied. Then following all that would be a closing plenary session in which we try and bring closure to some of the issues that were discussed and propose next steps. That's what I had. Dr. Thompson.

DR. THOMPSON: The only thing addition that I had was that -- a suggestion to also discuss ongoing changes to the model and application to existing products, in terms of one of the breakout sessions. That was the only other point I had.

DR. SUNDLOF: Dr. Carnevale, did you want to comment?

DR. CARNEVALE: No, I think you captured it.

DR. SUNDLOF: Thank you. Our next speaker was Richard Wood from Food Animal Concerns Trust. He was concerned about the timeliness and the speed at which we were moving forward on this issue, indicating that we had originally talked about responding to the comments by April and that we start responding to the comments. He stressed public accountability; for instance, who is in charge, who is going to be making the decision, what are the deadlines.

Questions at workshops, when will we get some of the answers that CVM has promised. There was a number of process questions. He indicated that they would like to know what CVM is planning, that we lay out our plan for addressing some of the issues that pertain to the risk assessment and the Framework Document.

He questioned whether the risk assessment should include any risk -- any threshold for risk of a drug in Category I. There was a concern that drug sale and use data, which were part of the Framework Document, they are not specifically mentioned anywhere and he was wondering where we are on that.

Thresholds; who will be at the table when the decisions are made, experts, consumers, et cetera. He wanted clarification on who would be at the table. Dr. Thompson indicated she didn't have anything else. Mr. Wood.

MR. WOOD: Fine. Thank you.

DR. SUNDLOF: Okay. Thank you. Then Robert Dodemaide

offered a personal opinion. He indicated that experts at the meeting should include members from the American Association of Bovine Practitioners, American Association of Swine Practitioners, and poultry pathologists. Do you have anything?

(No audible response)

DR. SUNDLOF: Robert, does that cover it?

MR. DODEMAIDE: (Nods head affirmatively)

DR. SUNDLOF: Then Tom Schilark spoke as representative from the NCCLS. He indicated that a presentation should be made by NCCLS to discuss the process in which they develop these breakpoints for veterinary drugs, and maybe even some human drugs should be presented at the workshop, as a way of bringing people up to speed. Tom, was there anything else?

MR. SCHILARK: That was it. That was fine.

DR. SUNDLOF: Okay. Patti Leiberman from CSPI. Dr. Leiberman said that CVM needs to develop a sense of urgency, pretty much was in agreement with the comments made by Richard Wood that we didn't seem to be moving as fast as they would like. There has been no response to CSPI's current citizens' petition. The categorization she felt needed to be in place before we entered into the discussion on setting thresholds. I had something about the risk assessment, but I didn't put anything down. Experts in public health, consumer groups, and EU policy should be present at the meeting. That is all I had. Did you have any addition?

DR. THOMPSON: Just a comment with regard to approval of additional virginiamycin combination subs.

DR. SUNDLOF: Yes. Dr. Leiberman.

DR. LEIBERMAN: (Nods head affirmatively)

DR. SUNDLOF: Okay. Thank you. Dr. Al Sheldon from Center for Drug Evaluation and Research at FDA supported European experts -- by the way, let me just add that if you have names of these European experts, please include those in the comments, because that would be helpful for us. And that there should be microbiologists from the FDA to provide information on how to set interpretive criteria for breakpoints, that process, understanding that process would be helpful in the discussion. Al, did you have anything?

DR. SHELDON: No.

DR. SUNDLOF: Thank you. Then Dr. Fred Angulo from CDC spoke. He indicated that there was a need for clarity on the implementation dates that was also a theme carried out by -- or that was expressed by Richard Wood and Patti Leiberman, and that categorization would be helpful prior to the discussion on thresholds, another issue that CSPI also spoke to. Got it?

DR. ANGULO: (Nods head affirmatively)

DR. SUNDLOF: Okay. Thanks, Fred. Then Joe Unowski from CDER, FDA, indicated that categorization is genetically linked to other antimicrobials and that some of the experts that would be appropriate for the committee -- for the workshop at least in December should be genetic experts to address this issue.

MR. UNOWSKI: (Away from microphone) Right. I see that as a risk factor.

DR. SUNDLOF: Risk factor.

MR. UNOWSKI: --- resistance also very ---.

DR. SUNDLOF: Again, if you know of people whose names you could submit, we would appreciate that.

MR. UNOWSKI: Sure.

DR. SUNDLOF: Pre-approval workshop. Let me go back. I think we got Dennis Wages. Dennis Wages representing AVMA and AABP, Dennis?

(No audible response)

DR. SUNDLOF: The American Veterinarian Medical Association and American Association of Bovine Practitioners, with a comment from Eric Geinder, was that --

DR. WAGES: Yes.

DR. SUNDLOF: -- a separate comment. Okay. Let me see if I can capture this. The AVMA commented that risk assessment is essential to determine if there is any effect of regulation, that is that unless you have done a risk assessment you will never know if your efforts to regulate have been successful or have any effect at all or made things worse. In addition, that there needed to be a cost benefit analysis conducted, so that the public understands the potential costs that restricting antimicrobials would have versus any perceived benefits. So it would be a risk analysis and a -- risk assessment and a cost benefit analysis.

Small shifts in susceptibility may not have any effect on increasing risk and that that needs to be taken into account.

Some experts that were suggested to come to the

meetings were Kathy Ewert from BARE and Dave Dargatz from USDA AFSCIA.

Then I had that we needed to -- they needed some clarification as to what the next steps should be, risk assessment and threshold determination. Is there an acceptable level of risk or is it zero, that was one of the questions that was being asked; if it's a zero risk, then why are we talking about this.

Then these are comments I am attributing to Eric Geinder from here. Eric Geinder is a veterinarian who works both for the turkey industry and the cattle industry, is that correct?

DR. WAGES: Swine. Turkey and swine.

DR. SUNDLOF: Swine.

DR. WAGES: Yes.

DR. SUNDLOF: Swine and poultry industry. He was concerned about are we really doing a risk assessment or is this risk reduction. I am not sure what the point was there, so maybe Dennis can speak to that. Some experts suggested were Dr. Harley Moon from Iowa State University and Dr. Lester Crawford from Georgetown University. The question was raised whether managing use in animals as we are proposing without taking commensurate approach in human medicine makes any sense, that without a parallel track on the human side he questioned the relevance of taking any action on the animal side. Also, Clyde Thornsbury was listed as an expert. There was some other information around that, and I didn't catch all of that. On the pre-approval issue, well, we'll get to the pre-approval issue later.

DR. THOMPSON: The only other thing, and I wasn't clear if this was relating to pre-approval, was on -- he recommended collecting samples from -- rather than on-farm, I understood from pre-packaged food.

DR. SUNDLOF: And then ---.

DR. WAGES: (Away from microphone) --- pre-approval.

DR. THOMPSON: Pre-approval.

DR. WAGES: I will submit these to you --

DR. THOMPSON: Okay.

DR. WAGES: -- because it's in writing, as they were written. So, because I was just some kind of messenger.

DR. THOMPSON: Okay.

DR. WAGES: ---

DR. THOMPSON: Okay.

DR. SUNDLOF: Okay. Well, yes, we just want to make sure everybody is in agreement on what we heard today. I am going to move over to -- unless there are additional comments, I'll move over to the pre-approval summary, pre-approval workshop summary of the comments.

Again, Dr. Carnevale from the Animal Health Institute spoke on this issue. He asked that we state the purpose for pre-approval studies, that we make it very clear why it is that we want pre-approval studies and what those studies are an attempt to provide us in terms of information that will be helpful in making a safety assessment.

Now, how will they be used in evaluating, how will those pre-approval studies actually be used within the regulatory

process for evaluating new animal drug applications. He thought that in terms of the experts that we should have, there should be presentation by people who have experience with the 55815 studies and their value. In other words, we have required some pre-approval studies for certain continuously fed antimicrobials in feed, and those studies, get people involved who have got experience in there, tell us where the strengths and the weaknesses of that approach has been over time.

Then an overview of the animal drug development process and a separate talk on -- that talks about from discovery to actual approval and marketing of the product and what all is involved in that, to give people a sense of the amount of effort that goes into that. Does that pretty much capture it, Rich?

DR. CARNEVALE: (Nods head affirmatively)

DR. SUNDLOF: Okay. Thank you. Then Richard Wood from Food Animal Concerns Trust said -- is concerned that pathogen load needs to be a part of the discussion and that whether it's in conjunction with the February meeting or at another meeting, it's an important issue and it needs to be addressed.

He again considered that we need to make sure that we are progressing in a timely manner, that it is an urgent issue for FDA and that we take it as such.

Finally, he asked the question of post-approval monitoring, where is it covered in the workshop, and that this is an issue that needs to be addressed. I think that is all I have. Richard, was that --

MR. WOOD: (Away from microphone) Yes. Just one

additional comment that really wasn't a prior comment I made. I don't know if you called ---, and that had to do with the process, the meeting process for both workshops. I think what I was driving at anyway is that if it is a round table format, that it not end at the round tables, that there be, perhaps with Dr. Carnevale's model, a final plenary or some session where there is a full table with discussion around that full table among all concerned parties.

(Pause)

DR. SUNDLOF: Okay. Yes. I was just consulting with Dr. Thompson to make sure I have the next steps right. We will keep the docket open. We do welcome everybody's comments. We will try and take what we've learned here today and summarize those and include that in the docket. Based on your comments, this will help us as we move forward to planning the meeting in December, and we will, I know we said this before, we will try and get the information out to you just as soon as we can. Again, this is the top priority for CVM. Resources are strained as it is, but we will do whatever we can to get both the risk assessment out and further information on this meeting out just as soon as possible. Once again I want to thank everybody for coming here today and participating in this important meeting.

(Whereupon, the meeting was adjourned at 3:30 p.m.)